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Ibogaine and its congeners are  $\sigma_2$  receptor-selective ligands with moderate affinityWayne D. Bowen<sup>a,\*</sup>, Bertold J. Vilner<sup>a</sup>, Wanda Williams<sup>a</sup>, Craig M. Bertha<sup>a</sup>,  
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Abstract

Ibogaine (12-methoxyibogamine) exhibited moderate affinity for  $\sigma_2$  sites ( $K_i = 201$  nM) and low affinity for  $\sigma_1$  sites ( $K_i = 8554$  nM), thus showing 43-fold selectivity for  $\sigma_2$  receptors. Tabernanthine (13-methoxyibogamine) and ( $\pm$ )-ibogamine had  $\sigma_2$   $K_i = 194$  nM and 137 nM, respectively. However, they showed 3- to 5-fold higher  $\sigma_1$  affinity compared to ibogaine, resulting in about 14-fold selectivity for  $\sigma_2$  sites over  $\sigma_1$ . A potential ibogaine metabolite, *O*-des-methyl-ibogaine, had markedly reduced  $\sigma_2$  affinity relative to ibogaine ( $K_i = 5,226$  nM) and also lacked significant affinity for  $\sigma_1$  sites. ( $\pm$ )-Coronaridine (( $\pm$ )-18-carbomethoxyibogamine) and harmaline (1-methyl-7-methoxy-3,4-dihydro- $\beta$ -carboline) lacked significant affinity for either  $\sigma$  subtype. Thus,  $\sigma_2$  receptors could play a role in the actions of ibogaine.

**Keywords:**  $\sigma$  Receptor; Ibogaine; (Subtype selectivity)

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Ibogaine (12-methoxyibogamine) is one of several indole alkaloids found in the shrub *Tabernanthe iboga* of central Africa. It has been shown to have psychotropic effects, and was initially used for its hallucinogenic properties. Anecdotal reports that ibogaine decreases drug craving in addicted users have been supported in several animal studies where ibogaine has been shown to reduce self-administration of both morphine and cocaine (Glick et al., 1994). On this basis, ibogaine is currently being investigated for its potential in treating drug abuse. The mechanism of action of ibogaine is not known since this compound has been shown to lack significant affinity for all examined neurotransmitter receptors and ion channels to date, with the exception of only weak affinity ( $K_i = 2080$

nM) at kappa ( $\kappa$ ) opioid receptors (Deecher et al., 1992).

We have recently demonstrated that sigma ( $\sigma$ ) receptors mediate morphologic and cytotoxic effects in cultured cell lines and in primary cultures of various regions of rat brain upon exposure to high doses of  $\sigma$  ligands (Bowen and Vilner, 1994; Vilner et al., 1995). High doses of ibogaine have also been shown to have neurotoxic effects, causing degeneration of Purkinje neurons and gliosis in the parasagittal zones of rat cerebellum (O'Hearn and Molliver, 1993). In view of this, along with reports that  $\sigma$  ligands can modulate the effects of cocaine (Witkin et al., 1993), we were prompted to investigate whether ibogaine and some of its congeners might have affinity for  $\sigma$  receptors.

$\sigma_1$  Receptors were labeled as described previously, using [ $^3$ H](+)-pentazocine and guinea pig brain membranes (Bowen et al., 1993).  $\sigma_2$  Receptors were labeled as previously described using rat liver membranes, a rich source of  $\sigma_2$  sites, and [ $^3$ H]DTG in the presence of 1  $\mu$ M dextrallorphan to mask  $\sigma_1$  receptors (Helle-

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Table 1  
Affinities of ibogaine and related indole alkaloids at  $\sigma_1$  and  $\sigma_2$  receptors

| Compound               | $K_i$ (nM)                                                        |                                                                | $\sigma_1 K_i / \sigma_2 K_i$ |
|------------------------|-------------------------------------------------------------------|----------------------------------------------------------------|-------------------------------|
|                        | $\sigma_1$<br>[ $^3\text{H}$ ](+)-Pentazocine<br>Guinea pig brain | $\sigma_2$<br>[ $^3\text{H}$ ]DTG + dextralorphan<br>Rat liver |                               |
| Ibogaine               | 8554 $\pm$ 1134                                                   | 201 $\pm$ 23                                                   | 42.6                          |
| Tabernanthine          | 2872 $\pm$ 37                                                     | 194 $\pm$ 10                                                   | 14.8                          |
| ( $\pm$ )-Ibogamine    | 1835 $\pm$ 131                                                    | 137 $\pm$ 13                                                   | 13.4                          |
| O-des-methyl-Ibogaine  | 15006 $\pm$ 898                                                   | 5226 $\pm$ 1426                                                | 2.9                           |
| ( $\pm$ )-Coronaridine | 35688 $\pm$ 2858                                                  | > 26000                                                        | –                             |
| Harmaline              | 5447 $\pm$ 65                                                     | 19816 $\pm$ 675                                                | 0.27                          |

Membranes were prepared and radioligand binding assays carried out as previously described (Bowen et al., 1993; Hellewell et al., 1994). Twelve concentrations of unlabeled test ligand ranging from 0.05 nM to 10000 nM or 0.5 nM to 100000 nM were incubated with guinea pig brain membranes and 3 nM [ $^3\text{H}$ ](+)-pentazocine ( $\sigma_1$  receptors) or with rat liver membranes and 5 nM [ $^3\text{H}$ ]DTG in the presence of 1  $\mu\text{M}$  dextralorphan ( $\sigma_2$  receptors). Non-specific binding for both assays was determined in the presence of 10  $\mu\text{M}$  haloperidol.  $\text{IC}_{50}$  values were determined using the iterative curve-fitting program GraphPAD InPlot (San Diego, CA, USA).  $\text{IC}_{50}$  values were then converted to apparent  $K_i$  values using the Cheng-Prusoff equation. Values are the averages of 2–4 experiments,  $\pm$ S.E.M. Each experiment was carried out in duplicate.

well et al., 1994). Ibogaine hydrochloride and harmaline hydrochloride (1-methyl-7-methoxy-3,4-dihydro- $\beta$ -carboline hydrochloride) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). ( $\pm$ )-Ibogamine, tabernanthine (13-methoxyibogamine), and ( $\pm$ )-coronaridine (( $\pm$ )-18-carbomethoxyibogamine) were obtained as described previously (Deecher et al., 1992; Glick et al., 1994). O-des-methyl-Ibogaine was synthesized by demethylation of parent ibogaine using boron tribromide (C. Bertha, unpublished procedure).

The results are shown in Table 1. Ibogaine had low affinity for  $\sigma_1$  receptors but exhibited moderate affinity for  $\sigma_2$  sites, having 43-fold selectivity for the latter. Tabernanthine differs from ibogaine in the position of the methoxy group on the indole phenyl ring (C-13 vs. C-12), whereas ibogamine lacks phenyl ring substitution. Tabernanthine and ( $\pm$ )-ibogamine showed similar affinity for  $\sigma_2$  sites as ibogaine, but slightly higher affinity for  $\sigma_1$  sites. These results show that the methoxy group is not critical for  $\sigma_2$  binding activity. However, O-des-methyl-ibogaine, a probable ibogaine metabolite, had greatly reduced (24-fold lower) affinity for the  $\sigma_2$  site compared to ibogaine itself. This suggests that compared to the methoxy group, the more polar phenolic hydroxy group may not be well tolerated in the  $\sigma_2$  binding site. ( $\pm$ )-Coronaridine and harmaline, a structurally related  $\beta$ -carboline, lacked  $\sigma$  affinity, indicating a role of the ibogaine saturated ring system in  $\sigma$  binding.

These results show that ibogaine and two of its congeners, tabernanthine and ( $\pm$ )-ibogamine, are relatively selective  $\sigma_2$  receptor ligands, with moderate  $\sigma_2$  affinity ( $K_i = 137$ –201 nM). Ibogaine's  $\sigma_2$  affinity is higher than at any other receptor reported to date. In addition, results with the potential ibogaine metabolite, O-des-methyl-ibogaine, suggest that demethylation in vivo would eliminate  $\sigma$  binding activity and therefore

would terminate any actions of ibogaine which might be mediated by  $\sigma_2$  sites. As previously observed with other  $\sigma$  receptor ligands (Bowen and Vilner, 1994; Vilner et al., 1995), initial studies have shown that micromolar concentrations of ibogaine produce morphological changes and cell death in rat C6 glioma, human SK-N-SH neuroblastoma, and mixed primary culture of rat cerebellum (in preparation). Thus, the possible role of  $\sigma_2$  receptors in the behavioral and/or neurotoxic effects of ibogaine in vivo deserve further investigation. These data also suggest that ibogaine congeners may be good leads in the development of better  $\sigma_2$ -selective ligands.

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